The Neurobiology of Virtual Reality Pain Attenuation

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ABSTRACT

During the past decade, virtual reality (VR) has gained recognition as a means of attenuating pain during medical procedures. However, while investigators have examined the effects of virtual environments on level of distraction, subjective pain intensity, and brain activity, there have been only a handful of investigations into the neurobiological mechanisms associated with VR’s efficacy. In an effort to explain how VR may alter pain perception and produce analgesia, as well as to guide the development of novel and improved VR pain treatments, this review aims to link the wealth of empirical data examining the neurobiology of pain to the growing field of VR. This review is separated into three main sections: (a) a brief overview of the current literature on the use of VR for the treatment of pain; (b) a review of the basic neurobiology of how pain is detected, processed, and controlled by the brain; and (c) an exploration into how current VR pain treatments may impact the pain system to produce analgesia. In addition, the future of VR for pain treatment is discussed, including how current treatments might be improved and novel ways to use VR to treat pain might be developed. Speculation on future VR interventions is based on our current understanding of how the brain processes pain and how VR appears to alter this process and produce analgesia.

INTRODUCTION

OVER THE PAST 10 YEARS, virtual reality (VR) has been shown to be a powerful clinical tool for a variety of medical, psychological, and behavioral applications. In particular, VR has been used with great success to manage acute pain in patients undergoing routine and invasive medical interventions. The primary and senior authors of this paper recently cochaired a workshop on VR and pain at the 2006 CyberTherapy Conference, which concluded that VR holds considerable promise not only in pain management but also in training clinicians to more effectively treat pain. It was agreed that the recent success in the use of VR to manage pain comprises only a small fraction of VR’s potential for pain treatment.

Though the field of VR pain attenuation is still in its infancy, the past 50 years have been a time of great discovery in understanding and controlling pain. Early studies by Beecher1 revealed that pain is a subjective phenomenon and is only loosely related to a particular injury or bodily insult. In 1965, Melzack and Wall2 proposed the gate control theory (GCT), postulating that pain signals are not simply transmitted from the periphery to the brain but are modulated along the way. Later studies by Mayer et al.3 demonstrated that this modulation includes the activation of an elaborate ascending pain-control system that descends from areas in the

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midbrain and brain stem to pain pathways in the spinal cord. Around the same time, it was discovered that endogenous opioids and opioid receptors are present at varying levels throughout the brain and the descending pain-control system.6,7 This discovery provided profound insight into the analgesic actions of opioids, which had been recognized but not understood for centuries.

Today, we understand more fully the ways in which pain is transmitted and perceived, altered by drugs, and modulated by the brain. Chronic pain, for instance, results from a complex interplay between molecular, cellular, psychological (e.g., expectations, attitudes, individual history), and social (e.g., social context, cultural norms) factors.6 Furthermore, pain is modulated not only by neurons but also by glial cells, which are no longer relegated to menial supportive roles.7,8 Rather than attempting to uncover the mechanisms underlying effective treatments for pain, as was the case with our understanding of opioids, we can now design potential treatments based on our understanding of the complex pain system.

VR is one such area of particular promise in the treatment of pain. While VR has been used for various educational and research purposes for more than 15 years, it is only recently that the technology has been modified for use in clinical settings. By diverting attention away from the symptoms associated with painful medical interventions and instead immersing the participant in a virtual environment, VR can profoundly alter pain perception in diverse clinical situations. Early case studies in adolescent burn victims provided preliminary evidence that entering an immersive virtual environment acts as a potent nonpharmacologic analgesic during daily burn wound care.9 Likewise, a variety of controlled clinical studies have investigated and confirmed the efficacy of VR during painful and invasive medical procedures, including physical therapy in burn victims,10,11 pediatric outpatient chemotherapy,12 lumbar puncture,13 and pediatric IV placement.14

Despite the observed clinical efficacy of VR, little attention has been focused on the neurobiological mechanisms underlying the impact of VR on pain perception. Given the heterogeneity of pain perception, which depends not only on the particular noxious stimulus but also on the subject’s ethnicity, age, gender, emotional and attentional states, and past experiences with pain, it is critical that we understand the mechanisms that underlie VR’s actions in order to fully realize its potential as a treatment for pain.

**DISCUSSION**

**VR and pain attenuation**

Distraction has received considerable attention as an effective means of managing pain during both acute (e.g., venipuncture) and invasive (e.g., chemotherapy, burn wound care) medical procedures. While traditional distraction techniques are still useful, recent technological advances in the field of VR have opened doors to substantially more engaging modes of pain management. Immersive VR, a relatively new medium of human–computer interaction, allows the user to become an active participant in a virtual environment through visual, auditory, and tactile cues. By diverting attention from an unpleasant medical setting to a pleasant and absorbing virtual world, while also engaging higher cognitive and emotional centers of the nervous system, VR can markedly diminish a patient’s subjective pain experience. In contrast to other forms of distraction (e.g., cognitive tasks, movies), VR is a particularly effective means of attenuating pain because of its highly immersive nature. The presentation of VR through a helmet prevents the user from interacting with the world outside the virtual environment by limiting unrelated visual and auditory cues. Furthermore, unlike many other forms of distraction, VR may provide the user with a sense of “presence,” an impression that he or she is a part of the virtual world, which further enhances the immersive experience.15

Although the field and study of VR pain management is still in its infancy, a number of clinical case studies and randomized controlled trials provide strong support for the efficacy and feasibility of VR as a means of diminishing pain in medical settings. The earliest use of VR in a clinical setting was by Ramachandran and Rogers-Ramachandran,16 who created a “virtual reality mirror box” to investigate the effects of visual input on phantom limb sensations. In this paradigm, movement of a subject’s uninjured hand or arm produced an image that, to the subject, appeared as movement of the phantom limb. Of the 10 patients recruited into the study, six reported kinesthetic sensations in their phantom limb after viewing a mirror image of movement in their uninjured hand. Furthermore, five patients who frequently experienced painful “clenching spasms” in their phantom hand were able to relieve the pain when the mirror box was used to facilitate “opening” of the phantom hand. These early findings laid the critical groundwork for future studies investigating the impact of visual perception and VR on pain sensation.
Several years later, in a study of wound care in two adolescent burn victims, Hoffman et al. provided the first evidence that entering an immersive virtual environment can produce profound nonpharmacologic analgesic effects. Despite the excruciating pain associated with burn wound care, both subjects reported significant decreases in pain ratings when using VR compared to a less-immersive video game distraction paradigm. Several additional case studies provide further evidence suggesting that VR can substantially reduce pain during daily wound care and physical therapy in burn victims.

The potential use of VR as a nonpharmacologic analgesic has been explored in a variety of other clinical settings. In one case study, Hoffman et al. observed that VR immersion markedly reduced dental pain during periodontal scaling and root planning in two patients suffering from adult periodontitis. Likewise, Steele et al. provided the first evidence that VR can effectively diminish postoperative pain in children in a report describing a 16-year-old patient with cerebral palsy. Gershon et al. explored the use of VR for reducing procedural pain and anxiety in a pediatric cancer patient, again to great success. Finally, a recent study demonstrated the effectiveness of VR as an adjunctive pain control during transurethral microwave thermotherapy in an elderly male patient with benign prostatic hypertrophy.

Controlled group studies have further demonstrated the benefits of VR in medical settings. In several studies of pediatric and adult burn victims, researchers confirmed that VR significantly reduces pain during physical therapy, both when administered alone and when coupled with pharmacological analgesia. Hoffman et al. also observed that the analgesic effectiveness of VR did not decrease over three sessions of use. The results of two studies by Schneider et al. indicate that VR is also effective and feasible as a means of reducing pain and distress during outpatient chemotherapy in children and during chemotherapy for breast cancer in adult women. Notably, adult participants in the second study experienced a significant time-elapsed compression effect. Additional randomized studies have demonstrated the effectiveness of VR in pain management in a variety of medical circumstances, including adolescents with cancer undergoing lumbar puncture, pediatric oncology patients requiring invasive medical procedures, children receiving presurgical anesthesia, children undergoing routine outpatient venipuncture, pediatric patients undergoing venipuncture and wound care in the emergency department, and children requiring IV placement for magnetic resonance imaging (MRI) and computed tomography (CT) scan.

VR has also been studied as a method of attenuating pain during application of experimentally induced painful stimuli. Hoffman et al. investigated the neural correlates of VR pain attenuation by exposing study participants to periods of VR or no VR while enduring experimentally induced thermal pain in a functional MRI (fMRI). VR not only significantly reduced subjective pain scores but also diminished pain-related brain activity in five regions associated with pain sensation. Several additional studies of clinically healthy subjects undergoing experimentally induced ischemia have demonstrated that VR can increase pain tolerance, decrease self-reported pain intensity, and reduce the affective unpleasantness and time spent thinking about pain.

Despite substantial evidence from case studies and randomized trials attesting to the value of VR as a clinical tool, it is not well understood how VR impacts pain perception. In order to more fully understand the mechanisms by which VR modulates pain, however, we must first review our current understanding of the neurobiology of pain.

**VR and the neurobiology of pain**

Whereas much attention is paid to halting maladaptive pain, pain itself is an extremely important sense. Individuals born without the ability to perceive pain sustain numerous injuries and lead challenging lives, for they are unable to efficiently detect potential tissue damage. The ability to sense and respond to pain is critical not only for an individual’s survival but also for the survival of the species. It is thus not surprising that nature has provided elaborate pain detection, perception, and modulation systems.

Under normal conditions, pain is detected by nociceptors, which are located throughout the body (e.g., in skin, muscles, and organs). Nociceptors respond to stimuli that may indicate tissue damage and relay this information toward the central nervous system (CNS) via two types of neurons, A-delta fibers and C fibers. A-delta fibers are myelinated and have rapid conduction velocities of up to 30 m per second. Speed is essential in these fibers because they transmit pain signals that are perceived as sharp or burning. C fibers, on the other hand, are unmyelinated and send their signals at much slower conduction velocities of approximately 0.5–2 m per second. These fibers are not involved in the rapid notification of a painful bodily
insult but instead are responsible for the dull and aching pain of many chronic pain conditions as well as the secondary pain associated with acute pain. C fibers likely evolved as a means of encouraging an organism to guard or protect itself following injury or during sickness, allowing for more efficacious rehabilitation.

Both A-delta fibers and C fibers make their first synapse in the dorsal horn of the spinal cord (or trigeminal nucleus in the case of head pain). These pain signal–carrying fibers then cross at the midline, ascend in the spinal thalamic tract, and terminate in thalamus. Some pain signals also ascend in the spinomesencephalic tract and the dorsal column pathway. At the level of the brain, pain fibers innervate various cortical regions, including the primary and secondary somatosensory cortices, the anterior cingulate cortex (ACC), areas of the limbic system, and the insular cortex (see Figure 1).

Analgesia, the attenuation of painful sensations during consciousness, can be achieved by interrupting the body’s normal means of detecting pain. Traditionally, C fibers have been a primary target for analgesic development. Nonsteroidal anti-inflammatory drugs (NSAIDs), for example, block the production of prostaglandins, which are involved in C fiber activation and pain. Various topical pain treatments (e.g., capsaicin cream) also dampen C fiber activation. It is unlikely, however, that VR produces analgesia via direct effects on C fiber signaling.

On the other hand, rather than halting the pain signal through C fiber inactivation, many effective therapies, including deep brain stimulation, various analgesic drugs, and hypnosis, act within the brain to produce analgesia. While VR may also act within the brain, its mechanisms are likely different from other known pain interventions. By acting directly and indirectly on pain perception and signaling through attention, emotion, concentration, memory, and other senses (e.g., touch, auditory, visual), VR may change the activity of the body’s intricate pain modulation system, thus altering pain perception.

During the mid-twentieth century, the work of Beecher presented the earliest evidence suggesting that a variety of psychological variables can modify a person’s perception of pain. For example, Beecher observed substantial variations in soldiers’ responses to similar injuries, with some soldiers reporting little or no pain following battle despite significant insult. Melzack and Wall proposed the GCT of pain, which lent further support to the notion that various CNS activities (notably attention, emotion, and memory) can play a significant role in sensory perception. This theory asserted that pain signals are not simply passed from the periphery to the brain, but rather “nerve gates” determine the degree to which the pain sensation enters an individual’s awareness. Mechanistically, pain fiber inhibition can be achieved through activation of neurons carrying touch signals, which inhibit pain fibers in the spinal cord. This is why, for example, rubbing a sore area of the body can sometimes reduce pain in that area. Similarly, transcutaneous electrical nerve stimulation (TENS) is thought to produce analgesia by electrically stimulating touch fibers, which in turn inhibit pain signaling.

Building on the hypotheses proposed in the GCT, Mayer et al. demonstrated the existence of an intricate descending pain-control system originating in the brain. Chemical or electrical activation of this system via the fibers descending from the periaqueductal gray (PAG) area of the midbrain produced pronounced analgesia in animal models by inhibiting pain signals at the spinal level. Around the same time, endogenous opioid receptors and

**FIG. 1.** Graphic representation of the major known components of the ascending pain pathway (solid lines) and the descending pain-modulatory system (dotted lines). Functional connections between the ascending and descending pathways are not well established and, for the purposes of this review, are not depicted. ACC, anterior cingulate cortex; Hyp, hypothalamus; PAG, periaqueductal gray.
endogenous opioids \(^4,43\) were also discovered. Microinjection of opioid agonists into the descending pain-control system produced analgesia. \(^44\) Further, the analgesia produced by electrical stimulation of the PAG was blocked by antagonism of opioid receptors with naloxone. \(^45\)

Since the 1970s, research has focused on understanding the structure and function of the descending pain-control system (Figure 1). The discovery that the PAG receives inputs from a variety of areas of the brain, notably cortical regions involved in attention \(^46\) and emotion, \(^47–49\) suggests that modulation of the descending pain-control system may underlie the profound effects of attention and emotion on pain perception. Interestingly, in addition to inhibiting the transmission of pain signals, the descending pain-control system can also facilitate pain transmission. \(^50\) This noteworthy finding may help explain why hypervigilance and emotional concerns about pain often produce a heightened pain experience.

**Attention, VR, and pain**

Much of VR’s therapeutic power is derived from its ability to divert attention away from painful medical interventions and instead immerse an individual in an engrossing computer-generated environment through use of visual, auditory, and tactile cues. It is well documented that a variety of distraction paradigms (e.g., cognitive tasks, music) can be used to diminish a person’s subjective perception of pain. Using fMRI to monitor brain activity during pain distraction, studies \(^51–53\) have demonstrated that cortical areas associated with attentional processes and pain modulation are more active during distraction, whereas areas associated with pain perception are less active. Specifically, the PAG, perigenual ACC, and orbitofrontal cortex display increased activation during pain with distraction relative to pain alone, as measured by fMRI. \(^53\) In contrast, areas of the pain matrix (e.g., thalamus, insular cortex, and midcingulate ACC) display decreased activation during a cognitive distraction task. These observations suggest that pain distraction involves an inhibitory process and may implicate descending pain-modulation pathways.

The ACC is one region of particular importance in understanding the way in which VR may mediate pain perception. The ACC, a complex cortical structure located around the rostrum of the corpus callosum, has been subdivided into two distinct regions based on structure and function. \(^54\) The midcingulate ACC is activated during demanding cognitive tasks, whereas the perigenual ACC mediates attentional processes and emotional reactions to pain. \(^52\) In support of the ACC’s complex role in attention, emotion, and pain perception, Bantick et al. \(^52\) observed increased activity in the perigenual cingulate during a pain distraction task and a corresponding decrease in activity of the midcingulate. These changes in relative activity, which were associated with diminished pain sensation, suggest that the two regions may be reciprocally inhibiting. \(^55\) Furthermore, deCharms et al. \(^56\) recently demonstrated that activation of the perigenual cingulate (using fMRI feedback to control this brain activity) produced analgesia.

Alterations in activity of the ACC during pain distraction, however, do not fully elucidate the mechanism by which VR modulates pain perception. It is known that the ACC sends projections to a variety of brain regions, notably the midbrain PAG. \(^46\) Based on our knowledge of the descending pain-modulation pathway, which can be activated by PAG stimulation, it is reasonable to hypothesize that the ACC acts as a critical component of the VR-mediated pain-modulation pathway by exerting effects on structures known to modulate pain, such as the PAG. By diverting attention from an unpleasant medical setting to a highly immersive virtual environment, VR activates the perigenual ACC, a structure known to mediate attentional and emotional processes. The perigenual ACC may then activate its downstream target, the PAG, which in turn initiates a cascade of signaling events to stimulate the descending pain-modulation system and produce analgesia.

Although the role of the ACC in pain modulation and perception is not completely understood, the ACC is involved in attending to and ignoring pain. Furthermore, the ACC can modulate activity of the descending pain-control system and impact pain perception. Based on our knowledge of the neurobiology of pain, it is highly likely that VR acts through the ACC to divert attention away from pain and produce analgesia.

**Emotion, VR, and pain**

Like attention, emotion can also profoundly impact pain perception via the descending pain-control system. The amygdala, the primary structure of the limbic system, interacts with both the ACC and the PAG such that activation of the amygdala can produce either inhibition or facilitation of pain perception (Figure 1). In a recent review of the literature, Neugebauer et al. \(^57\) provide evidence suggesting that some negative emotions (e.g., fear, stress) activate a particular portion of the amygdala, re-
resulting in activation of inhibitory pain-control pathways. Other negative emotions (e.g., anxiety, depression), however, have the opposite effect and promote the facilitation of pain. Positive emotions, on the other hand, may inhibit the portion of the amygdala that facilitates pain, resulting in analgesia. In a recent study of emotional modulation of pain, Rhudy et al.\textsuperscript{58} observed that subjects exposed to pleasant images during the application of unpredictable noxious stimuli reported a decrease in subjective pain relative to those exposed to neutral or unpleasant images.

Because of its uniquely immersive nature, VR is a powerful means of modifying affect. Fears, anxieties, and cravings can be elicited or inhibited by specific VR environments. Positive affect can also be achieved using VR. Given the paucity of research into the neural correlates of emotion-modulated pain perception, we can hypothesize that the emotional component of VR may further modulate pain by means of the connections between the amygdala, the ACC, and the PAG. A better understanding of how emotions and pain interact may aid in the development of new VR environments that more effectively elicit positive affect and inhibit pain.

\textit{VR and pain attenuation: future directions}

While the efficacy and feasibility of VR as an adjunctive pain-management tool are clinically evident, research has only just begun to explore the complex neural mechanisms underlying the impact of VR on pain perception. Accordingly, future research in this new but rapidly growing field should strive to clarify the neurobiological means by which VR modulates pain perception. Studies employing fMRI to monitor brain activity during pain application and VR attenuation, for instance, continue to enhance our understanding of VR in exciting and sometimes unexpected ways. Additionally, future studies might explore the role of endogenous opioidergic signaling during VR pain attenuation by using opioid receptor antagonists (e.g., naloxone). We might hypothesize that antagonism of opioidergic signaling during VR pain attenuation would prevent VR-induced reductions in pain perception. Given that opioid receptor antagonists have been shown to inhibit the analgesic effects produced by PAG stimulation, this novel investigation could reveal whether VR is truly acting through the PAG and its downstream targets.

In addition, although the VR environments used thus far in clinical and experimental settings have proven effective, future research should strive to understand how the specific features of a VR environment affect the pain outcome. VR environments may prove to be more powerful if they are individually tailored to match patient characteristics such as age, gender, ethnicity, and personal interests, as well as the nature of the acute injury or medical intervention. A “cold” VR environment (e.g., an environment depicting snow and ice), for example, might prove more beneficial to a burn victim than a “hot” VR environment. Likewise, future research might explore whether VR more effectively diminishes pain if the participant plays an active (e.g., throws snowballs) versus passive (e.g., looks at scenery) role in the VR environment. With a better understanding of how specific features of a VR environment impact pain perception, we may be able to more effectively reduce pain in patients undergoing acute and invasive medical procedures.

While VR has shown efficacy in the management of acute pain, research has not yet examined the value of VR for the treatment of chronic pain, which affects approximately 50 million Americans. The current model of VR use in acute pain settings is not appropriate for chronic pain applications, for continual use of a VR helmet is neither reasonable nor desirable. Patients with chronic pain, however, report daily changes in their pain perception with regard to numerous factors (e.g., pain quality and intensity, frequency, duration). With the development of less expensive and portable VR systems, patients with chronic pain may be able to use portable or personal computer-based VR systems to manage bouts of severe pain. In addition to helping chronic pain sufferers manage breakthrough pain, VR treatment of chronic pain may also lessen the user’s dependence on opioids and other pharmacological interventions. Given that both pain\textsuperscript{59} and treatment with opioids\textsuperscript{60} can themselves produce subsequent pain and allodynia, by reducing the severity of bouts of pain and lessening the need for opioids, VR pain management may result in an overall reduction in the chronic pain state, even between times when VR is applied.

\textbf{CONCLUSIONS}

During the past decade, VR has proved to be a highly effective means of managing acute pain in a variety of medical settings. Yet despite its clinical efficacy, the neurobiological mechanisms underlying VR’s action remain enigmatic. By applying knowledge gained from a wealth of research on pain perception to the field of VR therapy, we can begin to understand the complex ways in which VR may
modulate the body’s endogenous pain perception system. Although recent research using fMRI provides additional insight into the analgesic effects of VR, future research in this rapidly growing field will further clarify the intricate neurobiological mechanisms underlying VR pain attenuation. Future studies that target neurobiological correlates of pain attenuation will also enhance our appreciation of the dynamic interplay between the biological and psychological (e.g., attention, memory, emotion) factors implicated in pain perception. A greater understanding of these processes will not only advance the science of pain attenuation and provide clinicians with additional modes of treatment for acute and chronic pain states but may lead to the development of new and more effective clinical applications of VR.

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